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Paper 10
Entered: August 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN LABORATORIES LIMITED,
Petitioner,

v.

AVENTIS PHARMA S.A.,
Patent Owner.

Case IPR2016-00627
Patent 5,847,170

Before: BRIAN P. MURPHY, TINA E. HULSE, and CHRISTOPHER M. KAISER, *Administrative Patent Judges.*

MURPHY, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Mylan Laboratories Limited ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1 and 2 of U.S. Patent No. 5,847,170 (Ex. 1001, "the '170 patent"). Paper 3 ("Pet."). Aventis Pharma S.A. ("Patent Owner"), filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). We have statutory authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Petitioner challenges claims 1 and 2 of the '170 patent as unpatentable under 35 U.S.C. § 103(a). Pet. 13–14. Based on the arguments and evidence presented in the Petition and Preliminary Response, we are not persuaded there is a reasonable likelihood Petitioner would prevail with respect to at least one of the claims challenged in the Petition. Therefore, we decline to institute *inter partes* review.

A. Related Proceedings

Petitioner identifies the following as related district court proceedings in the District of New Jersey regarding the '170 patent: *Sanofi-Aventis U.S. LLC, Aventis Pharma S.A. and Sanofi v. Mylan Laboratories Ltd.*, C. A. No. 3:15-cv-00290 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-07869 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Accord Healthcare, Inc.*, C. A. No. 14-08079 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. BPI Labs, LLC et al.*, C. A. No. 14-08081 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Fresenius Kabi USA, LLC*, C. A. No. 14-08082 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Apotex Corp. et al.*, C. A. No. 15-0287 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et*

al. v. Breckenridge Pharmaceutical, Inc., C. A. No. 15-0289 (MAS)(LHG); *Sanofi-Aventis U.S. LLC et al. v. Mylan Laboratories Limited*, C. A. No. 15-0290 (MAS)(LHG); and *Sanofi-Aventis U.S. LLC et al. v. Actavis LLC et al.*, C. A. No. 15-0776 (MAS)(LHG). Pet. 12–13.

B. Proposed Grounds of Unpatentability

Petitioner advances two grounds of unpatentability under 35 U.S.C. § 103(a) in relation to the challenged claims in the '170 patent:

Reference[s]	**Statutory Basis**	**Challenged Claims**
Kant (Ex. 1005)[1] in view of Klein (Ex. 1006)[2]	§ 103	1 and 2
Colin (Ex. 1007)[3] in view of Klein and Kant	§ 103	1 and 2

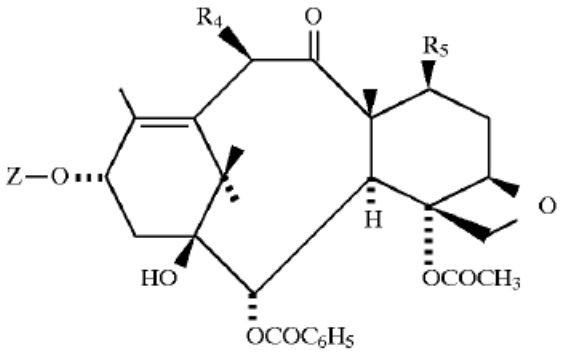
Pet. 13–14. Petitioner supports its challenge with a Declaration by Eric N. Jacobsen, Ph.D. ("Jacobsen Decl."). Ex. 1002.

C. The '170 Patent

The '170 patent, titled "Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them," issued December 8, 1998,

[1] Kant et al., *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III Synthesis and Biological Properties of Novel C-10 Taxol® Analogues*, Tetrahedron Letters, 35 (31), 5543–46 (1994) ("Kant"). Ex. 1005.
[2] Klein et al., Ch. 20 *Chemistry and Antitumor Activity of 9(R)-Dihydrotaxanes in Taxane Cancer Agents*, ACS Symposium Series Vol. 58, 276–287 (Georg et al., eds., 1994). Ex. 1006.
[3] U.S. Patent No. 4,814,470 issued March 21, 1989 to Colin et al. ("Colin"). Ex. 1007.

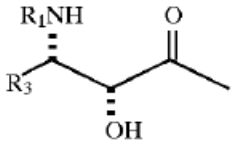
from an application filed March 26, 1996. Ex. 1001.[4] The '170 patent is directed to new taxoids of general formula (I):



(I)

in which:

Z represents a hydrogen atom or a radical of general formula (II):



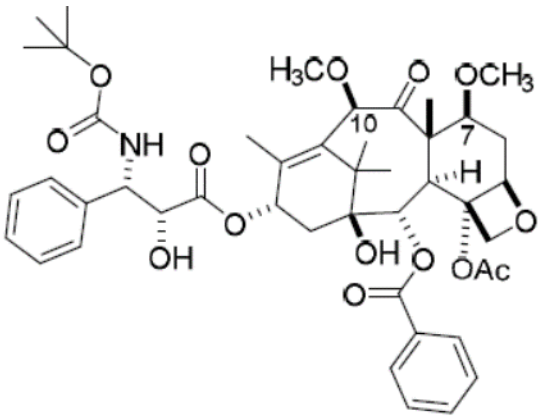
(II)

Ex. 1001, 1:7–28. The '170 patent discloses and claims, in particular, a compound known as cabazitaxel, pharmaceutical compositions containing cabazitaxel, and processes to prepare cabazitaxel. *Id.* at 12:52–13:33. The compounds of the '170 patent, including cabazitaxel, inhibit abnormal cell proliferation and have "antitumour properties, and more especially activity against tumours which are resistant to Taxol® or to Taxotere®."[5] *Id.* at 11:59–61, 26:32–37. Cabazitaxel is indicated for treatment of certain types of prostate cancer. Ex. 2002.

[4] The '170 patent claims priority to a provisional application dated January 17, 1996 and to French applications 95 03545 and 95 15381, dated March 27, 1995 and December 22, 1995, respectively. Ex. 1001, [60], [30].

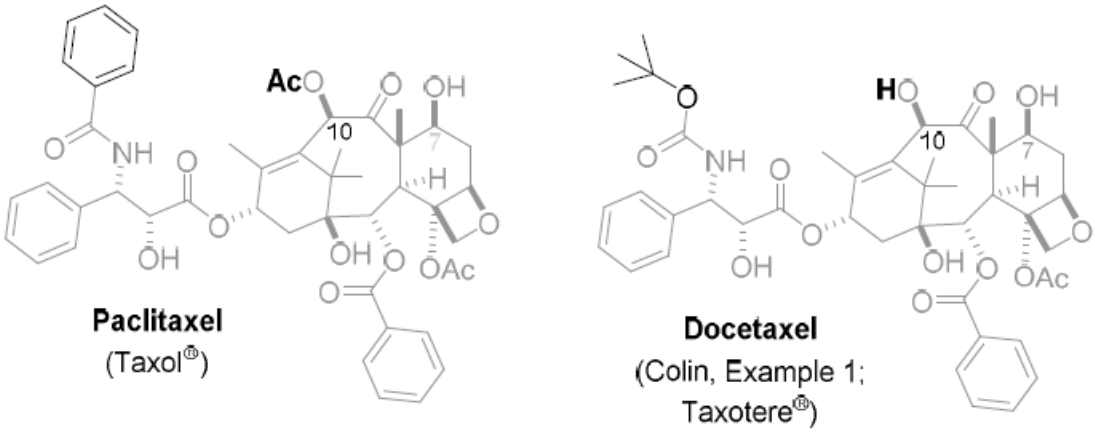
[5] Taxol® is the brand name for paclitaxel. Taxotere® is the brand name for docetaxel. We also refer to "Taxol" and "Taxotere" in this Decision.

The chemical name for cabazitaxel is 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-lβ-hydroxy-7β,10β-dimethoxy-9-oxo-ll-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate. *Id.* at 13:9–12, 28:57–60. The chemical structure of cabazitaxel is:



Pet. 3. Of particular interest in cabazitaxel are the presence of a methoxy group (OCH_3) at both the C-7 position (R_5 in formula I) and C-10 position (R_4 in formula I), and a carbonyl (C=O) at the C-9 position. Ex. 1001, 2:40–42, 3:1–3.

The prior art paclitaxel and docetaxel compound structures are shown below.



Pet. 9; Ex. 1002 ¶¶ 36–38. Paclitaxel and docetaxel are synthesized from a key "advanced precursor" known as 10-deacetyl baccatin III ("10-DAB").

Ex. 1002 ¶¶ 37–38. Paclitaxel has a different synthetic side chain (left side of molecule) than docetaxel, attached to the C-13 position of the core taxoid structure, and an acetyl (CH_3CO or "Ac") group rather than a hydroxyl (OH) group at C-10. In contrast to cabazitaxel, neither paclitaxel nor docetaxel has a methoxy group at C-7 or C-10, although both have a carbonyl at C-9. *Id.* Cabazitaxel has a docetaxel side chain (i.e., 3'-NHBOC or (3-tert-butoxycaronylamino)). *Id.* ¶¶ 11, 38.

D. Challenged Claims

Petitioner challenges claims 1 and 2 of the '170 patent, which are reproduced below:

> 1. 4α-acetoxy-2α-benzoyloxy-5β,20-epoxy-lβ-hydroxy-7β,10β-dimethoxy-9-oxo-ll-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.
>
> 2. A pharmaceutical composition comprising at least the product according to claim **1** in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.

II. ANALYSIS

A. Claim Construction

We determine that no claim terms require express construction for purposes of this Decision. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quotation omitted).

B. Asserted Obviousness of Claims 1 and 2 over Kant and Klein

Petitioner asserts that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a person of ordinary skill in the art

("POSA") based on the combined teachings of Kant and Klein. Pet. 29–38. Patent Owner opposes. Prelim. Resp. 18–38. We address the parties' arguments below.

1. Kant

Kant discloses a "chemoselective approach to functionalize the C-10 position of 10-deacetyl baccatin III [10-DAB], a key intermediate for the semi-synthesis of paclitaxel." Ex. 1005, 5543 (Abstract). Kant selects 10-DAB as "the ideal starting material" for synthesizing analogues of paclitaxel with the "aim of obtaining drugs having more desirable properties." *Id.* ¶¶ 2–3. Kant's reasoning is that "with the more reactive C-7 hydroxyl protected, an opportunity was available to *selectively deprotonate* the C-10 hydroxyl." *Id.* at 5544. Thus, Kant selectively introduced a variety of substituents at the C-10 position of 10-DAB to synthesize "a variety of C-10 paclitaxel analogues" shown in our annotated Table II, below.

Scheme 1

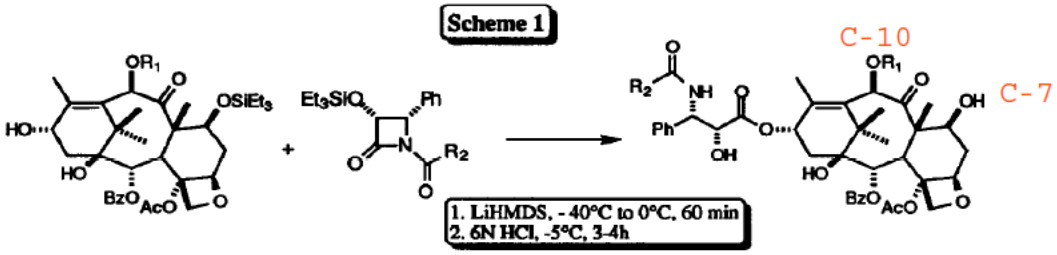


Table II

Paclitaxel Analogue	R_1	R_2	% Yield	Tubulin Ratio[a]	IC_{50} (nM)[b] HCT 116
Taxol®	Ph	Ph	-	1.0	2.0
15	COMe	OBu^t	80	0.7	2.0
16	COBu	Ph	78	1.5	3.4
17		Ph	85	1.1	2.3
18	$CON(Me)_2$	Ph	88	1.0	1.1
19	Me	Ph	73	1.0	12.0
20	Me	OBu^t	83	0.3	1.3
21	CO_2Me	Ph	76	1.1	3.0
22	CO_2Me	OBu^t	83	0.8	1.5
23	COPh	Ph	82	19	2.2
24	COPh	OBu^t	74	2.1	2.0

a=Ratio of analogue relative to paclitaxel ($EC_{0.01}$ @ 5 μM).

b=Drug concentration required to inhibit cell proliferation to 50% vs. untreated cells (incubated at 37°C for 72 h).

Id. at 5545. Kant Compound 20 contains a methoxy group at C-10 (R_1 is "Me" (methyl)), a hydroxyl group at C-7, a carbonyl at C-9, and a docetaxel side chain (R_2 is "OBu^t" (tert-butoxy)). *Id.* Kant concludes "it is reasonable to suggest that the functional group present at the C-10 position does modulate the antitumor activity, which is quite contrary to some of the earlier predictions." *Id.* at 5546.

2. Klein

Klein discloses 9(R)-dihydrotaxanes, a new family of compounds having "increased water solubility and stability as compared to taxol [paclitaxel] and also exhibit[ing] excellent activity in tumor models." Ex. 1006, 276 (Abstract). Klein highlights several advantages of replacing the C-9 carbonyl with a hydroxyl in both Taxol (paclitaxel) and Taxotere

(docetaxel): 1) the C-9 hydroxyl "serves as an additional site for modifications," 2) the C-9 hydroxyl "increase[s] the water solubility of these analogs," and 3) the absence of a C-9 carbonyl "stabilize[s] the system." *Id.* at 277. Klein discloses the synthesis of 9(R)-dihydrotaxol and 9(R)-dihydrotaxotere, which exhibit enhanced stability and aqueous solubility compared to paclitaxel and docetaxel due to the C-9 hydroxyl replacing the C-9 carbonyl, while maintaining "good efficacy." *Id.* at 279–280 (Table I).

Klein also experiments with substituting the C-7 and/or the C-9 hydroxyl groups with various alkylating substituents. *Id.* at 281. The experimental compounds include a methoxy group at C-9 (entry 7) or at C-7 (entries 8 and 10, with a hydroxyl at C-9), and all have an acetyl at C-10, as shown in our annotated Table III, below.

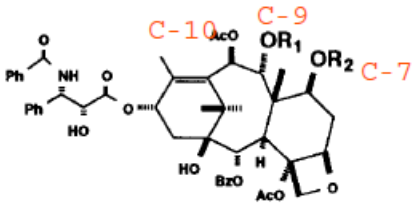
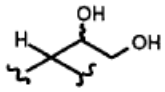
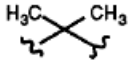


Table III. Tumor Cell Cytotoxicity of C-7,9 Analogs

Entry	Compound R_1 C-9	R_2 C-7	Tumor cell lines, IC_{50} (ng/mL) *A549*	*HT-29*	*B16F10*	*P388*
1.	H	H	16-22	6.4-9.6	25	49-57
	9-Dihydrotaxol 12					
2.	H	$CH_2CH(OH)CH_2OH$	>100	>100	>100	>100
3.	H	$CH_2CH_2NEt_2$	>100	>100	>100	>100
4.			>100	79	90	>100
5.			25	26	34	42
6.			19	11	20	35
7.	CH_3	H	4.7	3.1	4.8	7.8
8.	H	CH_3	1.2	1.4	1.5	3.9
9.	H	$CH_2CH=CH_2$	1	1.2	2.7	5.3
10.	H	CH_3 (3'-NBoc)	0.27	0.15	0.2	0.6

Id. at 281. Klein observes that the methylated C-7 analog in entry 10 exhibits "extremely potent cytotoxicity." *Id.* at 282.

3. Analysis

Petitioner acknowledges that "Kant does not describe the C-7 methoxy substitution needed to form" cabazitaxel.[6] Pet. 28. Petitioner further acknowledges that "Klein does not disclose the C-10 methoxy substitution" in cabazitaxel. *Id.* Petitioner argues, however, that a POSA would have selected Kant's Compound 20 "for further modification" (a so-

[6] Petitioner refers to cabazitaxel as 7,10-dimethoxy docetaxel. Pet. 28.

called "lead compound") because of its superior binding ability and cytotoxicity among the chemical analogues having the docetaxel side chain. Pet. 31 (citing Ex. 1002 ¶¶ 79–81). Petitioner reasons that a POSA would have modified Kant Compound 20 in view of Klein's Table III (compounds 8 and 10), teaching increased anti-tumor potency by substituting a methoxy group for a hydroxyl group at C-7, which would have led to the synthesis of cabazitaxel. *Id.* at 32–33.

We agree with Patent Owner that Petitioner's evidence is insufficient to establish a sufficient motivation for a POSA to have selected Kant's Compound 20 as a lead compound for further modification in view of Klein's Table III (compounds 8 and 10), to synthesize cabazitaxel with a reasonable expectation of success. Prelim. Resp. 20–37. For compositions containing new chemical compounds, there must have been a reason for a POSA to: (1) select the prior art "most promising to modify" (referred to as the "lead compound"), and (2) make all of the necessary modifications to arrive at the claimed invention. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012); *see also Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) ("[T]he attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art at the time the invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed invention."). There also must have been a "reasonable expectation" both of making the new compound, and of its advantageous properties. *Otsuka Pharm.*, 678 F.3d at 1292 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

a. Kant Compound 20 as a lead compound

We begin by observing that Kant uses 10-DAB as "the ideal starting material" to synthesize paclitaxel analogues by selective substitution at only the C-10 position. Ex. 1005, 5543 ¶ 3. Kant does not teach or suggest additional structural modifications to Compound 20 or docetaxel, which cuts against the notion of selecting Kant Compound 20 as a lead compound for further modification of this docetaxel analogue. Kant itself indicates the authors chose to use 10-DAB as the starting material for making selective C-10 substitutions in order to synthesize "novel paclitaxel analogues." *Id.*

We agree with Patent Owner that Petitioner also errs by starting with a hindsight-biased structural comparison of docetaxel, Kant Compound 20, and cabazitaxel in side-by-side fashion. Prelim. Resp. 31–34 (citing Pet. 31). As noted by Patent Owner, without a docetaxel control, Kant does not provide any information as to whether a particular compound performs better or worse than docetaxel. *Id.* at 33. Kant makes clear that the authors were synthesizing paclitaxel analogues and using paclitaxel, not docetaxel, as a control. Ex. 1005, 5545 Table II n.a (IC_{50} cytotoxicity measured as a "[r]atio of analogue relative to paclitaxel"). In addition to Compound 20, Kant also identifies Compound 22, which has a methyl carbonate group rather than a methoxy group at C-10, as more cytotoxic than paclitaxel or C-10 acetyl taxotere (docetaxel). Ex. 1005, 5546. Kant does not otherwise analyze the significance of the structural differences between Compounds 20 and 22 or the other synthesized compounds, apart from generally recognizing that the functional group at C-10 modulates antitumor activity. *Id.*

Kant also does not teach or suggest the possibility of simultaneous substitution of both the C-7 and C-10 positions, whether to increase potency and lipophilicity (cell membrane permeability) as argued by Petitioner (Pet. 21–22, 33), or for some other reason. Prelim. Resp. 20–26. Rather, Kant focuses on the possibility of improving anti-tumor cytotoxicity of paclitaxel analogues by *selective* substitution and functionalization of *only* the C-10 position, a point aptly made in the title, abstract, and text of Kant's article. Ex. 1005, 5543 ("a chemoselective approach to functionalize the C-10 position of 10-deacetyl baccatin III"), 5544 ("with the more reactive C-7 hydroxyl protected, an opportunity was available to *selectively deprotonate* the C-10 hydroxyl"), 5545 ("a variety of C-10 paclitaxel analogues were synthesized").

Patent Owner persuasively argues that Petitioner does not address why a POSA would have simultaneously modified the C-7 and C-10 positions in Kant Compound 20 to optimize lipophilicity, thereby minimizing aqueous solubility, when a POSA would have known docetaxel and paclitaxel were highly lipophilic and insoluble in water, which made their commercial formulation challenging. Prelim. Resp. 21–24 (citing Ex. 1006; Ex. 1011, 495 ("[Paclitaxel] is highly lipophilic and insoluble in water, but soluble in Cremophor EL, polyethylene glycols 300 and 400, chloroform, acetone, ethanol and methanol. For clinical use paclitaxel is formulated in 50% Cremophor EL and 50% dehydrated alcohol . . . . [Docetaxel] is insoluble in water . . . . The formulation used in the most recent clinical studies consists of 100% polysorbate 80."); Ex. 1015; Ex. 1019, 1:64–67; Ex. 1020, 206 ("Taxol is a promising antitumor agent with poor water solubility. Intravenous administration of a current taxol

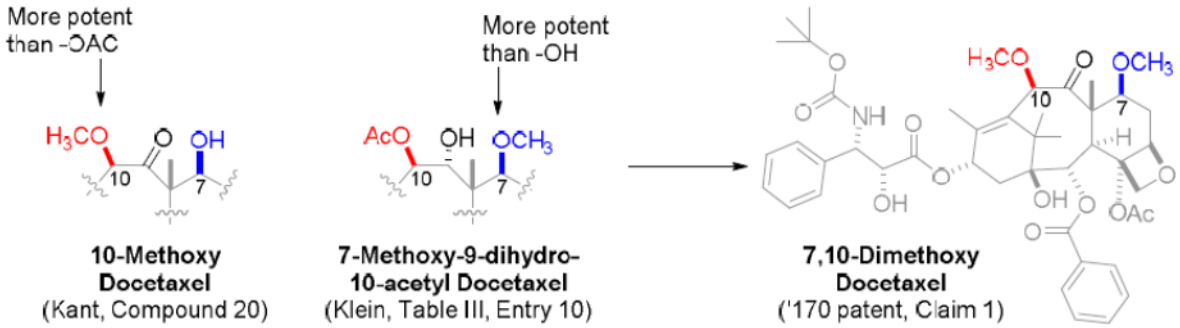
formulation in a non-aqueous vehicle containing Cremophor EL may cause allergic reaction and precipitation upon aqueous dilution. . . . The purpose of this study was to develop an aqueous based i.v. formulation of taxol that did not cause precipitation of the drug upon dilution and did not contain Cremophor EL."); Ex. 2004, 2:42–44; Ex. 2015, 648 ("Because of its limited aqueous solubility, it was necessary to formulate taxol in a vehicle consisting of 50% ethanol and 50% Cremophor EL (polyoxyethlated castor oil), a vehicle with known toxicity in dogs."); Ex. 2024, 45 ("Docetaxel . . . is practically insoluble in water but freely soluble in alcohol, and is currently formulated in polysorbate 80"); Ex. 2025, 91 ("[Paclitaxel's] poor water solubility poses delivery problems that have not been adequately resolved."); Ex. 2026, 996. Petitioner recognizes that alkylating the C-7 and C-10 functional groups would optimize lipophilicity (Pet. 22) but does not address the well-known problems with lipophilicity and limited aqueous solubility of intravenously administered paclitaxel and docetaxel. Therefore, we are not persuaded by Petitioner's argument that a POSA would have been motivated to optimize lipophilicity in a paclitaxel or docetaxel analogue via simultaneous substitution of the C-7 and C-10 positions.

For the reasons given above, there is insufficient evidence for us to conclude that a POSA would have selected Kant Compound 20 as a lead compound for further modification of both the C-7 and C-10 positions.

b. Rationale for further modifying Kant Compound 20 based on the teachings of Klein

We also are not persuaded by Petitioner's rationale and supporting evidence that a POSA would have modified Kant Compound 20 in view of Klein to make the required substitutions at C-7 and C-10 to synthesize

cabazitaxel. According to Petitioner, after selecting Kant Compound 20 for further modification, a POSA would have needed to make at least three more significant decisions to achieve the cabazitaxel structure from the teachings of Klein: 1) substitute Kant Compound 20's protected C-7 hydroxyl group with Klein's methoxy group, 2) retain Kant Compound 20's methoxy group at C-10 instead of Klein's C-10 acetyl group, and 3) retain Kant's carbonyl at C-9 instead of using Klein's C-9 hydroxyl to improve chemical stability and aqueous solubility of the compound. Pet. 32–34. Petitioner represents the proffered structural teachings below.



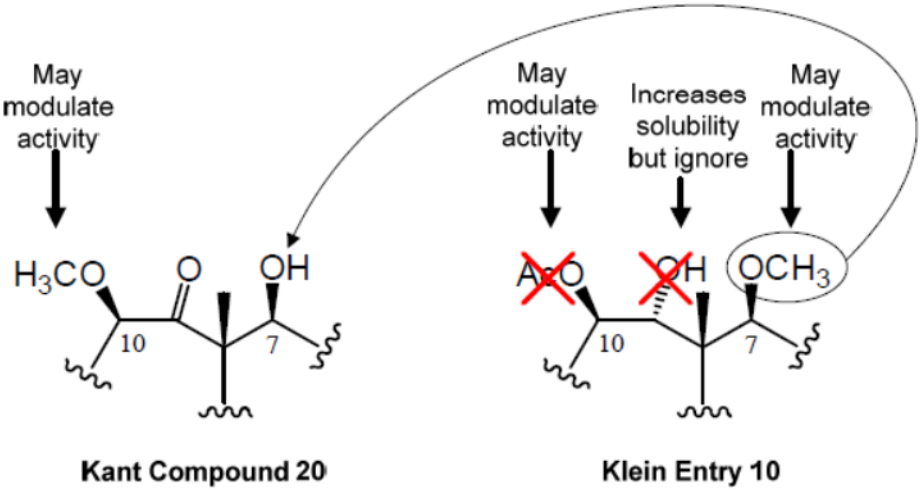
Id. at 32–33. The Petition, however, does not explain persuasively why a POSA would have disregarded two key teachings of Klein – i) increase aqueous solubility and chemical stability by reducing the C-9 carbonyl to a hydroxyl, and ii) maintain the C-10 acetyl (9-dihydrotaxol) to modulate activity while retaining good efficacy – in order to synthesize cabazitaxel from Kant Compound 20. Prelim. Resp. 27–30, 34–38 (citing Ex. 1006, 276–77); Ex. 1006, 279–280.

Klein expressly teaches the reduction of the C-9 carbonyl to a C-9 hydroxyl to increase aqueous solubility and chemical stability of the compounds, while maintaining "excellent in vivo activity in several solid

tumor models." Ex. 1006, 276; Prelim. Resp. 28 (citing Ex. 1006, 276–77). Petitioner argues that Klein teaches a "reduction at C-9 results in reduced potency" when compared to docetaxel (Pet. 34, 42-43), but the cytotocity data in Klein Table I shows that 9-Dihydrotaxotere (docetaxel with a C-9 hydroxyl) has comparable activity to docetaxel (Table I) and compound 10 (Table III) in at least 3 out of 4 cell lines. Ex. 1006, 280 (Table I), 281 (Table III). Klein, moreover, clearly teaches that "[t]hese products [*i.e.*, those with a C-9 hydroxyl] were shown to have excellent tubulin assembly activity and *similar in vitro activity* as compared to taxol and taxotere; therefore, these preliminary results establish that the *C-9 carbonyl is not required for activity*." *Id.* at 279 (emphasis added). Contrary to Petitioner's argument, Klein teaches that a C-9 carbonyl was not required to maintain anti-tumor activity and that reducing the C-9 carbonyl to a hydroxyl improves aqueous solubility and chemical stability of these notoriously insoluble compounds. *Id.* at 277, 279. Thus, we are not persuaded a POSA would have disregarded the improved aqueous solubility and stability provided by a C-9 hydroxyl, a key teaching in Klein, when considering possible modifications to Kant Compound 20.

We reach the same conclusion with respect to Klein's C-10 acetyl. Petitioner argues that a POSA would have retained Kant Compound 20's C-10 methoxy group over Klein's C-10 acetyl, because Kant teaches increased cytotoxicity of Compound 20 having a methoxy group at C-10 when compared to the C-10 acetyl of docetaxel (compound 15). Pet. 32–33 (citing Ex. 1005, 5546; Ex. 1002 ¶ 89). Klein, however, states that "facile deacetylation of the C-10 acetate is not trivial in the C-9 carbonyl series and reflects the greater stability of the 9(R)-dihydro series." Ex. 1006, 279.

Klein, therefore, does not necessarily teach or suggest replacing the C-10 acetyl unless the C-9 carbonyl is reduced to a hydroxyl group, such as in 9(R)-dihydrotaxotere. *Id.* We also are persuaded by Patent Owner's argument that Petitioner's analysis reflects improper hindsight by having a POSA select the C-7 methyl from compound 10 in Klein's Table III but reject the other teachings of Klein, as reflected in Patent Owner's diagram, reproduced below.



Prelim. Resp. 29.

Therefore, for the reasons given above, we are not persuaded Petitioner has established a reasonable likelihood of prevailing in its assertion that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a POSA over Kant and Klein.

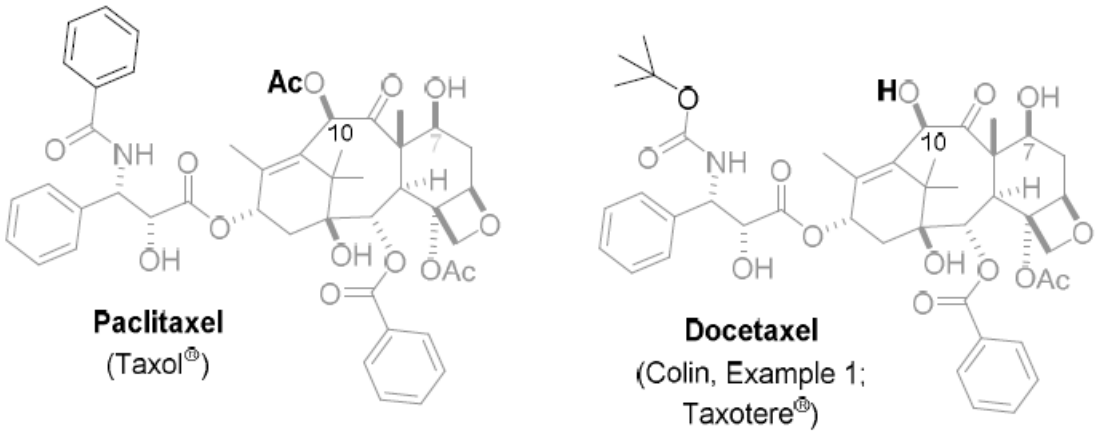
C. Asserted Obviousness of Claims 1 and 2 over Colin, Klein, and Kant

Petitioner asserts that the subject matter of claims 1 and 2 of the '170 patent would have been obvious to a POSA based on the combined teachings of Colin, Klein, and Kant. Pet. 38–49. Patent Owner opposes.

Prelim. Resp. 38–43. We incorporate our findings with respect to Klein and Kant and address the parties' arguments below.

1. Colin

Colin discloses four taxane compounds that are "useful anti-tumor agents." Ex. 1007, Abstract. Colin specifically describes docetaxel as having "valuable biological activities" and the four taxane compounds as being "approximately twice as active as taxol." *Id.* at 3:19-23, 3:29-30. The structure of docetaxel is shown below, to the right of paclitaxel.



Pet. 9; Ex. 1002 ¶ 71. As can be seen, docetaxel has a different side chain (3-tertbutoxycarbonylamino) from paclitaxel. Docetaxel has a hydroxyl group at C-7 and at C-10, and paclitaxel has a hydroxyl group at C-7 and an acetyl at C-10. Both have a carbonyl group at C-9. Colin discloses formulating docetaxel (the product of Example 1) for intravenous administration by dissolving it in Emulphor EL 620 (an emulsifier) and ethanol. *Id.* at 10:5–11.

2. Analysis

Petitioner argues that Colin discloses docetaxel and a reason for a POSA to select docetaxel as a lead compound for "further optimization,"

because docetaxel was known to have greater activity against various tumor cell lines and a longer elimination half-life when compared to paclitaxel. Pet. 8–9 (citing Ex. 1002 ¶¶ 70–71), 38–40 (citing Ex. 1011, 496 [497]; Ex. 1002 ¶¶ 98-103). Petitioner further argues that Klein and Kant provide sufficient reasons for a POSA to substitute the C-7 and C-10 hydroxyl groups in the docetaxel structure with methoxy groups, to achieve cabazitaxel with a reasonable expectation of success. Pet. 40–45 (citing Ex. 1002 ¶¶ 66, 84, 87–89, 102–117). Regardless of whether Colin's docetaxel would have been selected as a lead compound for further optimization, Petitioner's argument is insufficient for the same reasons articulated above. For example, Petitioner repeats the argument that a POSA would have sought to optimize docetaxel's cell membrane permeability by replacing the C-7 and C-10 hydroxyl groups with more lipophilic groups, without addressing the well-known difficulties of formulating highly lipophilic, water-insoluble paclitaxel and docetaxel into a useful intravenous dosage form. Pet. 40.

Petitioner further argues that Klein teaches methylation of the C-7 hydroxyl and acetylation of the C-10 hydroxyl to improve potency over a hydroxylated docetaxel analogue, but acknowledges that Klein compound 10 in Table III still contains "two minor" structural differences from cabazitaxel. *Id.* at 41–42. As explained above in section II.B.3.b. of this Decision, Petitioner does not address persuasively the question of why a POSA would have disregarded Klein's teachings to reduce the C-9 carbonyl to a hydroxyl group to improve aqueous solubility and chemical stability of the modified docetaxel compound, and to maintain a C-10 acetyl group with a hydroxylated C-9 to modulate biological activity of the compound. *Id.* at

42–43. Nor does Petitioner persuasively rationalize Kant's teaching of selective substitution at only the C-10 position to increase cytotoxicity, with Klein's teaching to functionalize the C-7 and/or C-9 positions, particularly given the absence in Kant of a docetaxel control. *Id.* at 44–45 (citing Ex. 1002 ¶¶ 91, 97, 107–108, 113–115, 117).

Weighing the evidence as a whole, Petitioner's argument that a POSA would have selectively methylated both the C-7 and C-10 positions of docetaxel to create a more potent analogue (cabazitaxel) based on the teachings of Klein and Kant, is not persuasive.[7]

III. CONCLUSION

Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to its assertions of obviousness of claims 1 and 2 of the '170 patent.

IV. ORDER

Accordingly, it is

ORDERED that the Petition is denied.

[7] In view of our Decision, we need not consider the parties' arguments and evidence regarding secondary considerations of nonobviousness. Pet. 49–50; Prelim. Resp. 44–53; *see Transocean Offshore Deepwater Drilling, Inc., v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) ("objective evidence of nonobviousness . . . may be sufficient to disprove or rebut a prima facie case of obviousness").

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